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Hyperglycaemia-Induced ROS and Immune Dysfunction: A Comprehensive Review

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ABSTRACT

Hyperglycaemia is a defining biochemical hallmark of diabetes mellitus and exerts profound effects on cellular redox homeostasis and immune function. Sustained elevations in blood glucose promote excessive generation of reactive oxygen species (ROS) through multiple mechanisms, including mitochondrial electron transport chain overload, activation of NADPH oxidases, advanced glycation end-product (AGE) formation, polyol pathway flux, and impaired antioxidant defenses. The resulting oxidative environment disrupts cellular signaling, damages biomolecules, and alters transcriptional programs essential for innate and adaptive immunity. Immune dysfunction under chronic hyperglycaemia involves impaired neutrophil chemotaxis and phagocytosis, dysfunctional macrophage polarization, aberrant antigen presentation, T-cell exhaustion, dysregulated cytokine production, and heightened susceptibility to infections. Moreover, immune dysregulation contributes to the chronic low-grade inflammation and tissue damage characteristic of diabetes complications, including atherosclerosis, nephropathy, neuropathy, and impaired wound healing. This review synthesizes current mechanistic insights into hyperglycaemia-induced ROS production and immune impairment, integrating evidence from molecular biology, clinical studies, and translational research. We also discuss therapeutic strategies targeting redox imbalance and immunometabolic pathways, highlighting emerging antioxidant, metabolic, and immunomodulatory interventions. By clarifying the interconnected roles of oxidative stress and immune dysfunction, this review underscores the importance of integrated metabolic-immune approaches in the prevention and management of diabetes and its complications.

Keywords: hyperglycaemia, reactive oxygen species, immune dysfunction, oxidative stress, diabetes complications

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycaemia arising from impaired insulin secretion, insulin resistance, or both[1]. Beyond glucose toxicity, hyperglycaemia triggers a cascade of biochemical disturbances that compromise cellular integrity and immune function. One of the most critical mediators of this pathology is reactive oxygen species (ROS)-highly reactive molecules that, when produced in excess, disrupt redox homeostasis and impair biological processes essential for immune surveillance, tissue repair, and metabolic regulation[2]. In recent decades, diabetes has been increasingly conceptualized as both a metabolic and immune disorder. The interplay between hyperglycaemia-driven oxidative stress and immune dysregulation is now recognized as a key nexus in the pathogenesis of chronic diabetes complications and the heightened infection susceptibility observed in diabetic patients[3]. Understanding the molecular links between hyperglycaemia, ROS generation, inflammation, and immune dysfunction is therefore essential for advancing therapeutic strategies[4]. This comprehensive review explores the mechanisms by which hyperglycaemia induces ROS production, how oxidative stress disrupts innate and adaptive immunity, and the implications for diabetes progression and complications.

2. Mechanisms of Hyperglycaemia-Induced ROS Generation

Hyperglycaemia elevates intracellular ROS through multiple synergistic biochemical pathways that collectively overwhelm endogenous antioxidant mechanisms[5]. Persistent exposure to high glucose alters mitochondrial

metabolism, activates membrane-bound oxidase systems, promotes non-enzymatic glycation, and disrupts redox-regulating biochemical cycles[6]. These changes establish a sustained oxidative environment that contributes to cellular dysfunction, inflammation, and tissue injury across metabolic and immune systems.

2.1 Mitochondrial Overproduction of Superoxide

Excess glucose increases the supply of NADH and $FADH_2$ to the mitochondrial electron transport chain, raising membrane potential and causing electron leakage at complexes I and III[7]. Escaped electrons prematurely reduce oxygen to superoxide, which is then converted to hydrogen peroxide. When produced in excess, these species overwhelm detoxification pathways, induce mitochondrial DNA damage, impair ATP synthesis, and activate redox-sensitive transcription factors such as NF-κB[8]. This process establishes a central feed-forward source of oxidative stress in hyperglycaemic states.

2.2 Activation of NADPH Oxidases

Hyperglycaemia stimulates NADPH oxidase isoforms NOX1, NOX2, and NOX4, which are specialized enzymatic sources of ROS[9]. This activation is driven in part by protein kinase C, whose activity is upregulated by high glucose-induced diacylglycerol accumulation. NOX-derived ROS amplify mitochondrial ROS generation and contribute to endothelial dysfunction, impaired phagocyte activity, and propagation of inflammatory signaling[10].

2.3 Advanced Glycation End Products

Prolonged hyperglycaemia promotes the formation of advanced glycation end products, which modify proteins and lipids and interact with the receptor RAGE[11]. Binding of AGEs to RAGE activates intracellular ROS production and upregulates NF-κB, increasing expression of inflammatory cytokines, adhesion molecules, and chemokines[12]. This mechanism links metabolic stress with chronic inflammatory activation.

2.4 Polyol Pathway Flux

When intracellular glucose exceeds glycolytic capacity, it is diverted into the polyol pathway[13]. Aldose reductase converts glucose to sorbitol in a reaction that consumes NADPH, while sorbitol dehydrogenase subsequently generates fructose. Increased consumption of NADPH limits regeneration of reduced glutathione, weakening antioxidant capacity[14]. This depletion exacerbates oxidative stress and contributes to vascular and neural complications of diabetes.

2.5 Hexosamine Pathway and PKC Activation

Increased glucose availability enhances flux through the hexosamine biosynthetic pathway, resulting in elevated O-GlcNAcylation of various proteins[15]. These modifications can alter transcriptional regulation and reduce the activity of antioxidant enzymes such as superoxide dismutase and catalase[16]. Additionally, elevated diacylglycerol levels promote PKC activation, further stimulating NADPH oxidase–dependent ROS production and reinforcing redox imbalance.

2.6 Impaired Antioxidant Defense Systems

Chronic hyperglycaemia diminishes the expression and functional activity of key antioxidant enzymes, including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase[17]. Reduced synthesis and regeneration of glutathione lowers the cellular GSH/GSSG ratio, compromising the capacity to neutralize hydrogen peroxide and lipid peroxides[18]. As antioxidant reserves decline, cells become increasingly susceptible to oxidative injury, inflammation, and immune dysfunction.

3. Impact of ROS on Innate Immune Dysfunction

Excessive production of ROS in the context of chronic hyperglycaemia exerts widespread negative effects on the innate immune system, compromising the first line of defense against microbial invasion[19]. Innate immune cells depend on tightly regulated redox signaling for effective pathogen recognition, phagocytosis, antigen presentation, and cytotoxicity. When ROS levels exceed physiological thresholds, oxidative damage alters membrane integrity, protein function, and intracellular signaling pathways. These alterations not only reduce the efficiency of antimicrobial responses but also promote uncontrolled inflammation that contributes to diabetic complications[20]. The cumulative effect is a dysfunctional innate immune landscape characterized by impaired microbial clearance, heightened susceptibility to infections, and inadequate coordination with the adaptive immune system.

3.1 Neutrophil Dysfunction

Neutrophils are highly responsive phagocytes whose activity depends on dynamic cytoskeletal remodeling, receptor signaling, and controlled bursts of ROS during microbial killing[21]. Hyperglycaemia impairs chemotaxis by disrupting actin polymerization and interfering with chemokine receptor signaling, leading to delayed recruitment to infection sites. Oxidative modification of membrane receptors diminishes phagocytic capacity and reduces uptake of bacteria and fungi[22]. Dysregulation of NOX2 activity results in either insufficient oxidative burst, impairing intracellular killing, or excessive ROS release that injures surrounding

tissues[23]. These combined defects explain the high incidence of cellulitis, soft tissue infections, pneumonia, and urinary tract infections observed in individuals with poorly controlled diabetes.

3.2 Macrophage Polarization Imbalance

Macrophages require balanced ROS signaling to transition between pro-inflammatory M1 and reparative M2 phenotypes[24]. Chronic oxidative stress favors persistent M1-like polarization, characterized by increased production of TNF-α, IL-1β, IL-6, and other inflammatory mediators. At the same time, high ROS promotes mitochondrial dysfunction and impairs signaling pathways necessary for M2 differentiation, including STAT6 activation[25]. This imbalance hinders tissue repair, prolongs inflammation, and contributes to non-healing diabetic wounds and the progression of atherosclerotic lesions.

3.3 Dendritic Cell Dysfunction

Dendritic cells rely on redox-regulated processes for antigen uptake, processing, and presentation[26]. Hyperglycaemia impairs endocytic capacity and reduces expression of MHC class II molecules, CD80, and CD86, thereby weakening their ability to activate naïve T-cells. Altered cytokine production, particularly reduced IL-12 and increased oxidative suppression of IL-10 regulation, further diminishes their immunostimulatory function[27]. These changes lead to impaired T-cell priming, weakened antiviral and antibacterial responses, and poor coordination between innate and adaptive immunity.

3.4 Natural Killer Cell Impairment

NK cell cytotoxicity depends on intact granule exocytosis, perforin stability, and granzyme activation, all of which are sensitive to oxidative damage[28]. Excessive ROS disrupts these mechanisms, reducing the ability of NK cells to eliminate virus-infected and malignant cells. Hyperglycaemia also impairs NK cell receptor signaling, limiting their capacity to recognize abnormal cells[29]. As a result, individuals with diabetes experience increased vulnerability to viral infections and reduced tumor immune surveillance.

4. Therapeutic Approaches Targeting ROS and Immune Dysfunction

A range of therapeutic strategies aims to counteract hyperglycaemia-induced oxidative stress and the resulting immune imbalance[30]. Approaches span metabolic regulation, direct antioxidant support, enzyme-targeted therapies, and emerging immunomodulatory interventions. Together, these strategies target the interconnected pathways through which elevated glucose disrupts redox homeostasis and impairs innate and adaptive immunity[31].

4.1 Glycaemic Control

Optimizing blood glucose levels remains the foundational strategy for reducing ROS production at its source. Insulin therapy lowers intracellular glucose overload and prevents excessive mitochondrial electron flux[32]. Metformin reduces ROS through AMPK activation, improved mitochondrial efficiency, and decreased hepatic glucose output. SGLT2 inhibitors mitigate oxidative stress by lowering glucose exposure and reducing inflammatory cytokines, while GLP-1 receptor agonists improve metabolic control and exert direct anti-inflammatory effects. Effective glycaemic control slows progression of oxidative tissue injury and supports immune function.

4.2 Antioxidant Therapies

Antioxidant-based therapies represent an important complementary approach for mitigating hyperglycaemia-induced oxidative stress. Because ROS production arises from multiple cellular sources, a combination of dietary, pharmacological, and targeted mitochondrial antioxidants has been explored to restore redox balance[33]. These interventions not only reduce oxidative damage but also help normalize immune cell signaling, cytokine production, and pathogen-clearing capacity.

4.2.1 Dietary Antioxidants

Dietary antioxidants provide broad-spectrum free radical scavenging and enhance physiological antioxidant defenses. Vitamins C and E are classical examples: vitamin C functions as a water-soluble reductant that neutralizes superoxide and regenerates vitamin E, while vitamin E stabilizes lipid membranes and prevents lipid peroxidation[34]. Polyphenolic compounds such as curcumin, resveratrol, and quercetin exert anti-inflammatory effects by modulating NF-κB, Nrf2, and MAPK pathways, thereby protecting immune cells from oxidative injury. Carotenoids, including beta-carotene and lycopene, support membrane stability and quench singlet oxygen. Regular intake of these antioxidants has been associated with improved neutrophil function, enhanced macrophage phagocytosis, and reduced inflammatory cytokine secretion, making them valuable adjuncts in managing oxidative stress in diabetes.

4.2.2 Mitochondria-Targeted Antioxidants

Mitochondria are the principal intracellular source of ROS under hyperglycaemic conditions, making them key therapeutic targets. Agents such as MitoQ, SkQ1, and the SS31 peptide selectively accumulate within the mitochondrial matrix, where they intercept ROS before they trigger oxidative chain reactions[35]. These

molecules help maintain mitochondrial membrane potential, reduce electron transport chain leakage, and preserve ATP production. By stabilizing mitochondrial function, they improve the metabolic flexibility of immune cells, enhance antigen presentation, and restore balanced cytokine responses. Early clinical and preclinical studies indicate that mitochondrial antioxidants may reduce systemic inflammation and improve immune dynamics in metabolic diseases.

4.3 NADPH Oxidase Inhibitors

NADPH oxidase enzymes are major drivers of hyperglycaemia-induced ROS. Pharmacological inhibitors such as GKT137831 and apocynin specifically target NOX isoforms implicated in endothelial dysfunction and chronic inflammation[36]. By reducing NOX-derived superoxide, these agents lower oxidative burden in vascular and immune cells, improve nitric oxide bioavailability, and disrupt feed-forward ROS amplification loops. Their anti-inflammatory effects make them promising candidates for preventing diabetic vascular complications and modulating immune dysregulation.

4.4 Enhancing Endogenous Antioxidant Systems

Strengthening intrinsic antioxidant capacity provides a sustained defense against chronic oxidative stress. Activation of the Nrf2 transcription factor-through agents like sulforaphane, curcumin derivatives, or bardoxolone methyl-upregulates genes encoding glutathione synthesis enzymes, heme oxygenase-1, and NAD(P)H quinone oxidoreductase-1[37]. This enhances detoxification of ROS and supports immune cell survival under metabolic stress. Therapies that increase glutathione levels further bolster redox buffering and improve macrophage and dendritic cell function.

4.5 Immunomodulatory Interventions

Immune-targeted therapies are increasingly recognized for their role in correcting inflammation driven by oxidative stress. IL-1β antagonists and TNF-α inhibitors reduce excessive cytokine signaling that perpetuates ROS production and immune dysfunction[38]. In addition, emerging therapies targeting T-cell metabolic pathways aim to restore immune tolerance and reduce oxidative injury within lymphoid tissues. These immunomodulators complement antioxidant strategies by directly addressing the immune consequences of chronic ROS elevation in diabetes.

CONCLUSION

Hyperglycaemia-induced ROS generation is a central driver of immune dysfunction in diabetes. Excessive ROS disrupts the function of innate and adaptive immune cells, impairs wound healing, increases infection susceptibility, and fuels chronic inflammation and complications. Therapeutic strategies that integrate glycaemic control with redox and immunometabolic modulation hold great promise for improving outcomes in diabetic patients. Understanding these complex interactions remains essential for developing the next generation of targeted interventions.

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